Pulmonary function as a risk factor for dementia death

RESEARCH REPORT:

Pulmonary function as a risk factor for dementia death: an individual participant meta-analysis of six UK general population cohort studies

Running Head: Pulmonary function as a risk factor for dementia death

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Abstract word count: 244

Article word count: 2799

ABSTRACT

Background: In addition to being associated with all-cause mortality and cardiovascular disease mortality, lung function has been linked with dementia. However, existing studies typically provide imprecise estimates due to small numbers of outcome events and are based on unrepresentative samples of the general population.

Methods: Individual participant meta-analysis of six cohort studies from the Health Survey for England and the Scottish Health Survey (total N=54,671). Dementia-related mortality was identified by mention of dementia on any part of the death certificate (mean follow-up 11.7 years). Study-specific Cox proportional hazard models of the association between lung function and dementia-related death were pooled using random effect meta-analysis to produce overall results.

Results: There was a dose-response association between poorer lung function and a higher risk of dementia-related death (age- and sex-adjusted hazard ratio compared to highest quartile of forced expiratory volume in the first second (FEV_1), 95% confidence interval: second quartile 1.32, 0.99-1.76; third quartile 1.78, 1.30-2.43; fourth (lowest) quartile 2.74, 1.73-4.32). There was no significant heterogeneity in study-specific estimates (I^2=0%). Controlling for height, socioeconomic status, smoking, and general health attenuated but did not remove the association (second quartile 1.15, 0.82-1.62; third quartile 1.37, 0.96-1.94; fourth quartile 2.09, 1.17-3.71). Results for forced vital capacity (FVC) and peak flow were similar.

Conclusion: In these general population samples, the relation between three measures of lung function and dementia death followed a dose-response gradient. Being in the bottom quartile of lung function was associated with a doubling of the risk.

Keywords: Lung function, dementia, socioeconomic factors, meta-analysis

WHAT IS ALREADY KNOWN ON THIS SUBJECT?

Dementia is increasingly being acknowledged as a condition of major public health importance. Furthermore there is a growing recognition that exposures across the life course contribute to the risk of developing manifest dementia in later life. Lung function is a putative marker for potentially relevant life course exposures but studies linking it with dementia are scarce.

WHAT THIS STUDY ADDS

This large, general population-based study identifies a dose-response association between poorer lung function and the risk of dementia death with individuals at the bottom quartile of lung function having a two-fold increased risk compared to those at the top quartile. Further work examining the mechanism underlying this association may shed light on the aetiology of dementia and, ultimately, guide preventative strategies.

INTRODUCTION

Dementia is a major, growing public health priority affecting more than 800,000 people in the UK and 44 million worldwide.[1] Since there are still no disease-modifying treatments,[2] the focus of research has moved to prevention. However, modification of cardiovascular risk factors in late life does not reduce dementia risk.[3] This may relate to the slow development of the neuropathological processes of dementia which can begin years, or even decades, before the onset of symptoms[4-6] and, as a result, many now advocate the application of the life course paradigm to dementia epidemiology.[7] This approach suggests that exposures throughout life might have a detrimental or protective effect on disease risk.[8] In the absence of studies with follow up encompassing entire life-spans, identifying exposures which capture experiences from different stages of life are important in the investigation of life course effects on disease. For example, height – regarded as a marker of early life illness, adversity, nutrition or psychosocial stress[9] – has been shown to be associated with dementia.[10] Pulmonary function is also affected by multiple factors throughout the life course, not merely in early life, notably smoking, and it has been suggested that decreased lung function is linked to both cardiovascular disease[11 12] and cognitive decline,[13-19], as well as to overall mortality.[12 20 21] However, studies linking lung function and dementia are scarce[22-27] and the largest include around ten thousand participants. Few of these studies targeted the general population. Therefore we add to the limited evidence base the first meta-analysis of individual-participant data using six large general population cohort studies.

METHODS

Data source

The study sample comprised four Health Surveys for England[28] (1995-7 and 2001) and two Scottish Health Surveys[29] (1998 and 2003). These are annual (HSE) or intermittent (SHS), representative, general population-based cross-sectional studies sampling community-dwelling

individuals in the UK. The majority of study members (82.2%) consented to mortality surveillance by linkage to the UK National Health Service death register, thus converting the original cross-sectional studies into prospective cohort studies. Study participants gave full informed consent and ethical approval was granted for all aspects of these studies by the London Research Ethics Council or the Local Research Ethics Councils prior to each survey year data collection.

Measurement of lung function and covariables

Pulmonary function was measured using a Vitalograph spirometer. The spirometer was calibrated at the start of each day and the temperature in the survey participant's home entered prior to its use. Participants blew into the spirometer five times while standing up and the researcher recorded whether these were technically satisfactory blows. The highest value for forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), and peak flow (PF) was recorded.

Informants were visited by an interviewer, who measured height and weight – allowing computation of body mass index using the usual formula (weight[kg]/(height[m])^2) – and subsequently by a nurse. Ethnicity was coded as white, black, Asian, and 'Chinese or other'. Age upon leaving full-time education was recorded as <15, 15, 16, 17, 18, >18 years, 'never went to school', and 'still in full-time education'. Information on occupational social class was collected during the interview and coded according to the Registrar General classification (professional, intermediate, skilled non-manual, skilled manual, part-skilled, and unskilled), a standard approach in the UK. Smoking status was classified as never a regular smoker, ex-smoker, and smoker with daily consumption recorded. Alcohol consumption was recorded as frequency of drinking. During the interview, participants were asked to rate their health on a five-point scale (very

good/good/fair/bad/very bad) and asked whether or not they suffered from a long-standing illness.

Mortality data

Study participants were linked to mortality data until the first quarter 2011 and all causes recorded on death certificates (up to ten) were obtained in addition to date of death. Dementia was identified from death certification according to ICD-9 codes 290.0-290.4, 294.9, 331.0-331.2, and 331.9 and ICD-10 codes F00, F01, F03, F09, G30, and G31. Preliminary analyses suggested that using dementia as underlying cause of death gave the same results as using any mention of dementia but, due to fewer deaths, resulted in lower statistical power (Supplementary Table 1). Therefore, any mention of dementia in any part of the death certificate was used as the outcome of interest, a standard approach in dementia epidemiology since people with dementia often die of other conditions.[30-33]

Statistical analysis

After ascertaining that the proportional hazards assumption had not been violated we used Cox proportional hazards models[34] to compute study-specific effect estimates with accompanying standard errors for the association between pulmonary function and dementia-related death. We then pooled these study-specific estimates in random effects meta-analyses. We report hazard ratios (HR) with accompanying 95% confidence intervals (95% CI) for four categories of each marker of lung function in relation to dementia-related death. Lung function categories were defined created by choosing pulmonary function test cut-offs which provided an approximately equal number of dementia deaths in each category. Since preliminary results suggested a linear relationship between lung function and dementia death, we also report hazard ratios per standard deviation (SD) disadvantage (decrease) in pulmonary function. Calendar time (months) was the

underlying time scale; for participants who did not die from dementia, data were censored at the linkage date.

There was no effect modification by gender, so data for men and women were pooled and (age- and) sex-adjusted. Models were then additionally adjusted for a series of covariates: height, ethnicity, occupational social class, educational attainment, smoking, alcohol consumption, body mass index, self-rated general health, and longstanding illness. We then combined all these variables in a multivariable model. We compared the effects of controlling for different confounding and mediating variables on the magnitude of the association by examining the change in size of hazard ratio rather than a change in significance level.

We computed models examining the association between lung function and all-cause mortality for comparison with the dementia-related death models. We also carried out a number of sensitivity and subgroup analyses. We repeated the multivariable model restricting the sample to never-smokers. We also examined the effect on the multivariable model of excluding deaths occurring in the first five years of follow up to investigate the possibility that individuals with undiagnosed dementia might have found it more difficult to comply with pulmonary function testing. Individuals with data missing for one or more variable and those with no missing data were compared using Student's t-test for continuous variables and χ^2 tests for categorical variables. We then produced five multiply imputed datasets in SPSS version 21 and repeated the multivariable model using these data. All other analyses were conducted using R version 2.15.2. The reporting of our analyses conforms to the STROBE statement.[35]

RESULTS

Figure 1 shows the derivation of the sample used in these analyses. From an initial sample of 73,859 participants, 5,774 (7.8%) did not consent to record linkage and 13,414 (18.1%) were

missing essential data. This resulted in an analytic sample of 54,671 (mean [SD] age 46.8 [17.6] years). Supplementary Table 2 shows details of the individual cohort studies and comparisons between individuals who did and did not consent to mortality follow up are shown in Supplementary Table 3.

Table 1 shows the baseline characteristics of the sample by pulmonary function. Poorer lung function was generally associated with a less favourable risk factor profile: shorter stature, fewer remaining in education after the compulsory school leaving age, a higher proportion from a manual occupational social class, a larger proportion of smokers, slightly higher body mass index, a smaller proportion rating their health as good or very good, and a larger proportion with a longstanding illness. Individuals with poorer lung function were less likely to drink alcohol at least once weekly.

Of 7327 deaths during a mean (SD) follow up of 11.7 (3.7) years, 459 were dementia-related (139 where dementia was recorded as the underlying cause of death). The relationship between the different lung function tests was high (correlation coefficient range 0.77-0.92, all $p<0.001$; Supplementary Table 4); we therefore report only results for FEV_1 in relation to dementia death (Supplementary Table 5 shows the meta-analysis results for FVC and PF). Poorer FEV_1 was associated with increased risk of dementia death in a dose-response pattern (Figure 2 and Table 2): age- and sex-adjusted HR (95% CI) per SD decrease in FEV_1 1.65 (1.42, 1.93; $p<0.001$; Figure 3). Adjusting individually for height, educational attainment, occupational social class, smoking status and self-reported general health decreased the magnitude of this association somewhat; other covariates had negligible effects. Adjusting for groups of covariates (socioeconomic status, health behaviours, and illness) and multiple variables simultaneously further reduced the strength association but the association remained statistically significant (multivariable-adjusted HR per SD decrease in FEV_1, 95% CI: 1.43; 1.18, 1.72; $p<0.001$).

Sensitivity and subgroup analyses

We performed a series of subgroup analyses to ascertain the robustness of these associations (Supplementary Table 6). First, restricting the sample to never-smokers did not alter our conclusions, although the reduction in sample size reduced the statistical power of the analyses, making the dose-response association seen in the main results slightly less clear. Second, excluding deaths occurring within the first five years of follow up to explore reverse causality (the possibility that people in the early stages of dementia were less able to perform pulmonary function tests effectively) did not affect the observed association. Third, accounting for missing data by multiple imputation also did not change our findings. Individuals with missing data for one or more variables were slightly younger, more likely to be female, less likely to be white British, more likely to have more than compulsory education, more likely to have a manual occupation, more likely to smoke, less likely to drink alcohol at least once weekly, had a lower BMI, were less likely to rate their health as good or very good, and were more likely to have a longstanding illness than participants with complete data for all variables (Supplementary Table 7). Thus, individuals with missing data did not invariably have an unfavourable risk factor profile and the statistical significance of the differences is likely to relate, in part, to the large sample size.

DISCUSSION

We have shown a strong dose-response association between lung function and dementia-related death over an 11-year follow-up of six UK general population samples. Part of this association was accounted for by height, smoking, socioeconomic status, and self-reported general health but the association remained even after adjustment for these factors. Being in the bottom quartile of lung function was associated with a doubling of dementia-related death.

Comparison with other studies

Our findings are in agreement with previous results from smaller-scale studies. The association between decreasing lung function and mortality has been well-described.[12 20 21] However, there are fewer prospective studies linking pulmonary function with dementia. The largest study followed 10,211 men from 13 cohorts (including geographically-defined and occupational samples) over 40 years and identified 160 cases of dementia from death certification.[23] Participants in the highest quartile of FVC had better survival compared to the lowest quartile although the linear trend was not statistically significant (multivariable-adjusted HR; 95% CI: 0.54; 0.30, 0.98; p_{trend}=0.28). Another study followed 9837 people aged 47-70 over a median 14.1 years.[24] However, there was substantial attrition from the initial representative sample (N=15,792). They found worse survival in the lowest quartile of FEV_1 (multivariable-adjusted HR, 95% CI: 1.59; 0.91, 2.78; p_{trend}=0.03) and FVC (2.08; 1.16, 3.72; p_{trend}=0.006), compared to the highest quartile. Furthermore, the 205 dementia cases were identified from hospitalisation; while people with dementia are at an increased risk of hospitalisation,[30] the majority of diagnoses are made in the community, not everyone is admitted to hospital, and a dementia diagnosis is frequently missed on discharge.[36 37] Another study (N=9480) identified 2767 incident dementia cases over four decades follow up but found no association between pulmonary function and dementia. [25] The Age, Gene/Environment Susceptibility-Reykjavik Study (N=3,665), over 23 years, found an association between mid-life pulmonary function (FEV_1/height^2) and later dementia, diagnosed by a three-stage screening process (OR 0.68, 95% CI 0.55-0.84, P<0.001).[27] A study following 1291 women born in 1908, 1914, 1918, 1922 and 1930 systematically sampled from the census for 29 years, identified 147 cases based on clinical assessment.[22] The authors reported an association between all three measures of lung function used and dementia (multivariable-adjusted HR per SD increase in pulmonary function; 95% CI: peak flow 0.77; 0.65, 0.91; FVC 0.71; 0.57, 0.92; FEV_1 0.75; 0.59, 0.95). Only one of these studies included men and women and only one was truly representative of the general population,[25] the other having been subject to substantial attrition.[24]

Our findings are also in agreement with studies examining the relationship between pulmonary function and cognition, which is an aspect of dementia. The largest followed 3,036 Japanese-American men in Hawaii for at least 23 years and measured their cognition at the end of that time using the Cognitive Abilities Screening Instrument: baseline FEV_1 was a predictor of cognitive score in a linear regression.[18] Higher FEV_1 aged 43 in 1,778 men and women from the British 1946 birth cohort was associated with better psychomotor speed at that age as well as slower decline over ten years in psychomotor speed but not verbal ability or memory.[13] Another study of 1,192 men and women living in the community using structural equation modelling found that, in addition to education, strenuous activity and self-efficacy predicted cognitive change over two years.[17] A study of 857 men from Finland, the Netherlands, and Italy found that baseline lung function was associated with cognitive function at least 25 years later only in non-carriers of *APOE* ε4 ($p_{interaction}<0.05$).[14] A study assessing 832 male and female twins seven times over 19 years found changes in lung function were associated with subsequent cognitive change, particularly fluid cognitive abilities.[16] However, interpretation of studies looking at cognition at a single point in time are complicated by the fact that higher mental ability in childhood is associated with better lung function in later life.[15]

Strengths and limitations

The present study is by far the largest study to date of the association between lung function and dementia and is based on general-population samples. The use of individual participant meta-analysis adequately accounts for clustering within cohort studies. There has been minimal attrition due to the record linkage methodology.

However, there are a number of limitations in these data which must be acknowledged. While we were able to include a large number of important variables in our models, the possibility of

residual confounding remains. There was no information available on baseline cognitive function, respiratory illness or genetic factors in the HSE or SHS datasets. A further potential criticism is the use of dementia mortality as the outcome, though this has been used previously in another study of lung function and dementia.[23] The problems associated with the use of death certification in identifying dementia cases in observational studies include the unavoidable under-diagnosis of dementia in the community,[38] under-recording of dementia on death certificates,[39] and inaccurate coding of diagnoses. However, given the non-differential loss of data, it is likely that death certification is an adequate outcome for observational studies determining relative risk. A recent study found that almost three quarters of a memory clinic sample diagnosed with Alzheimer disease had dementia correctly recorded on their death certificates.[30]

Implications

Neither the sensitivity analysis in the present study nor a detailed previous longitudinal study[16] found evidence to suggest that the identified association between poorer lung function and dementia is attributable to reverse causality, but further research is needed to confirm this given the association between early life cognition and later life lung function.[15] The precise mechanisms underlying the association between lung function and dementia remain unclear. Dementia may share some aetiology with cardiovascular disease[40] and this overlap in the conditions may explain the association, since lung function is associated with cardiovascular disease.[11 12] Alternatively, it may be that lung function contributes to cognitive reserve, protecting against cognitive decline.[15] A further possibility is that, similarly to height, lung function may reflect life course exposures which also modify an individual's risk of dementia.[8 12] We have been able to include a number of possible candidates in our models as covariates, including smoking and early life socioeconomic status (educational attainment, albeit based on recall), but these factors did not fully explain the observed association. Other hypothesised

mechanisms for the association between pulmonary function and dementia include hypoperfusion and hypoxia affecting cerebral energy metabolism and leading to oxidative stress.[22] The finding that lung function is only associated with cognitive change in non-carriers of *APOE* ε4 may suggest a more complex relationship between pulmonary function and dementia.[14]

Conclusions

We have shown a dose-response association between poorer lung function and dementia-related death in a large, general population-based sample of men and women. Further research is required to characterise this association in more detail and to identify whether interventions to improve lung function can reduce dementia risk.

ACKNOWLEDGEMENTS

The Health Survey for England is part of a programme of surveys commissioned by The UK National Health Service Information Centre for health and social care, and carried out since 1994 by the Joint Health Surveys Unit of the National Centre for Social Research (NatCen) and the Department of Epidemiology and Public Health at the University College London Medical School. Supported by Alzheimer Scotland from 2009-2013, TCR is now employed by the University of Edinburgh and NHS Lothian. TCR, JMS and GDB are members of both the Alzheimer Scotland Dementia Research Centre funded by Alzheimer Scotland and of the University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology, part of the cross council Lifelong Health and Wellbeing Initiative (G0700704/84698). Funding from the BBSRC, EPSRC, ESRC, and MRC for the latter is gratefully acknowledged. ES is funded by a NIHR Career Development Fellowship and MK is supported by the Medical Research Council, UK (K013351), the US National Institutes of Health (R01HL036310; R01AG034454) and a professorial fellowship from the Economic and Social Research Council. All researchers are independent of funders who played no role in this study.

AUTHOR CONTRIBUTIONS: TCR conceived and designed the study. ES and GDB were responsible for acquisition of data. TCR and GDB were responsible for analysis and interpretation of data. TCR and GDB drafted the manuscript. All authors critically revised the manuscript for important intellectual content. TCR and GDB did the statistical analysis. GDB obtained funding. MK and GDB were responsible for study supervision. TCR and GDB are the study guarantors.

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FIGURE 1. Derivation of sample: individual participant meta-analysis (N = 54,671) of cohort studies from the Health Survey for England (N=4) and the Scottish Health Survey (N=2)

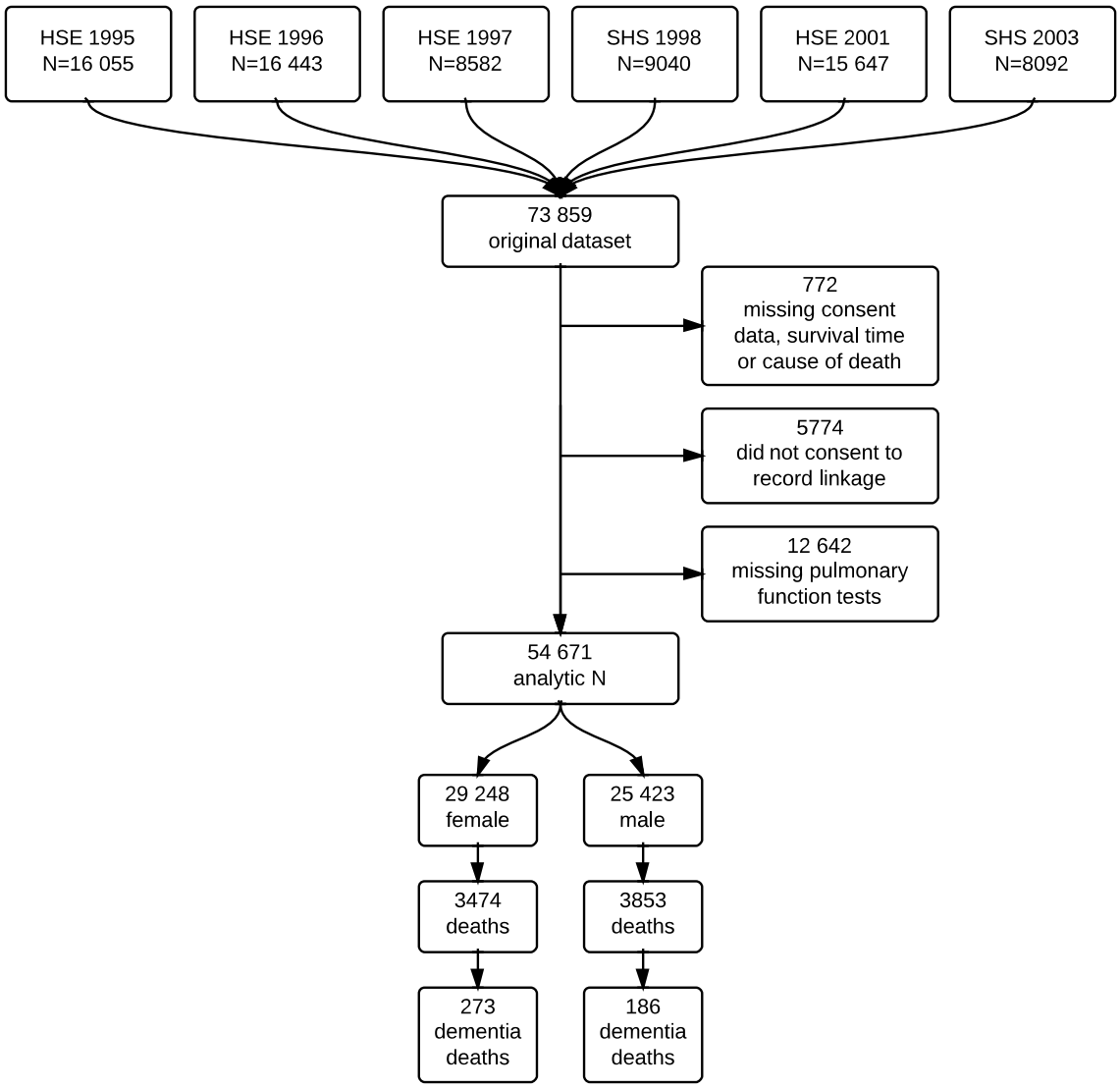
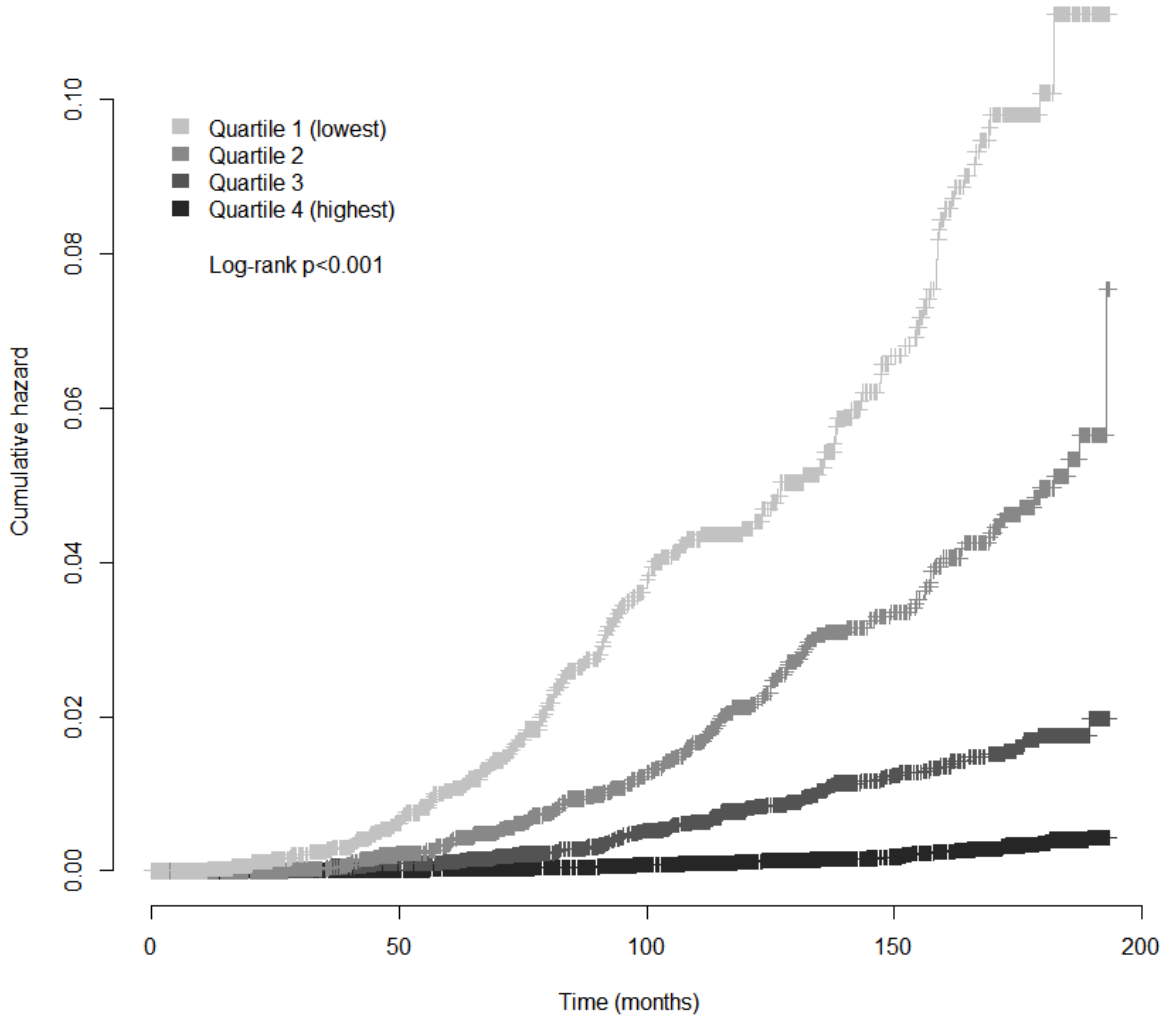


FIGURE 2. Kaplan-Meier cumulative hazard plot by FEV_1 quartile:[1] individual participant meta-analysis (N = 54,671) of cohort studies from the Health Survey for England (N=4) and the Scottish Health Survey (N=2)



[1] FEV_1 quartiles were defined using the following cut-points to give an approximately equal number of dementia deaths in each category: 1.36L, 1.81L, and 2.35L

FIGURE 3. Forest plot of the association between decreasing lung function (age- and sex-adjusted hazard ratio per standard deviation decrease in FEV_1) and dementia death: individual participant meta-analysis (N = 54,671) of cohort studies from the Health Survey for England (N=4) and the Scottish Health Survey (N=2)

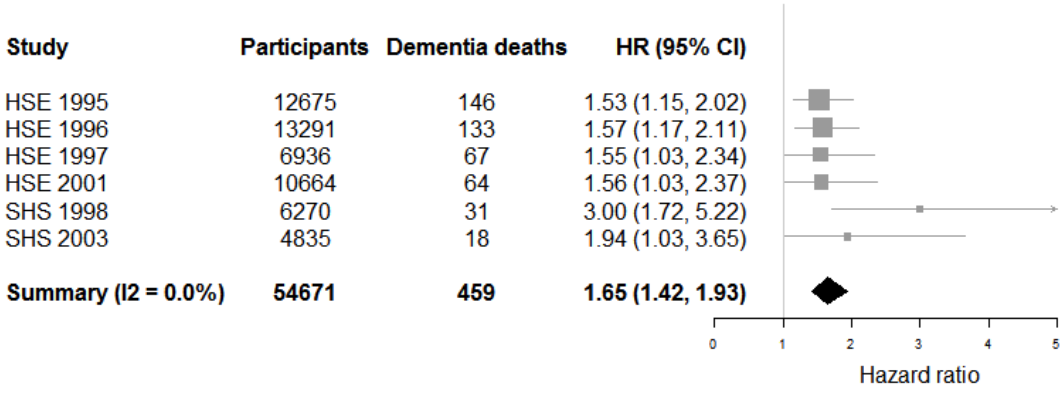


TABLE 1. Baseline characteristics of study members according to pulmonary function: individual participant meta-analysis (N = 54,671) of cohort studies from the Health Survey for England (N=4) and the Scottish Health Survey (N=2)

	FEV_1[a]				
	Q_1 (highest)	**Q_2**	**Q_3**	**Q_4 (lowest)**	**Total N[b]**
N	41279	7118	3569	2705	54671
Age [mean (SD)]	41.3 (15.0)	59.8 (13.5)	67.3 (12.1)	70.1 (13.2)	54671
Female (%)	46.2	75.4	78.9	73.9	54671
Height, cm [mean (SD)]	169.6 (8.9)	161.1 (7.4)	158.7 (7.7)	158.4 (9.0)	52571
Ethnicity (% white British)	96.0	94.4	95.2	97.1	54647
Left school ≥16 years (%)	73.5	39.6	29.4	25.9	54646
Non-manual social class (%)	58.4	53.5	47.1	42.5	51707
Never smoker (%)	48.5	43.2	42.1	34.5	54479
Drinks alcohol weekly or more often (%)	70.1	54.1	46.8	46.0	53614
Body mass index [mean (SD)]	26.2 (4.5)	27.6 (5.0)	27.8 (5.0)	26.9 (5.4)	51041
Self-rated health good or very good (%)	82.1	65.5	53.1	41.8	54660
Longstanding illness (%)	37.1	58.1	68.4	73.9	54663

[a] Cut-points used were 1.36L, 1.81L, and 2.35L to give approximately equal numbers of disease events in each group

[b] Total number of participants with complete data for each variable

TABLE 2. Hazard ratios (95% confidence intervals) for the association between FEV_1[a] and dementia-related death: individual participant meta-analysis (N = 54,671) of cohort studies from the Health Survey for England (N=4) and the Scottish Health Survey (N=2)

Models	Dementia deaths	N	Q_1 (highest)	Q_2	Q_3	Q_4 (lowest)	Per SD disadvantage	P for trend
Age- & sex-adjusted (basic model)	459	54671	1 (Ref.)	1.32 (0.99, 1.76)	1.78 (1.30, 2.43)	2.74 (1.73, 4.32)	1.65 (1.42, 1.93)	<0.001
+ Height	413	52571	1	1.19 (0.88, 1.61)	1.51 (1.08, 2.11)	2.19 (1.41, 3.42)	1.55 (1.30, 1.84)	<0.001
+ Ethnicity	459	54647	1	1.35 (1.01, 1.81)	1.82 (1.33, 2.48)	2.77 (1.77, 4.34)	1.68 (1.44, 1.96)	<0.001
+ Socioeconomic status[b]	444	51879	1	1.31 (0.91, 1.88)	1.60 (1.16, 2.19)	2.39 (1.40, 4.08)	1.50 (1.28, 1.77)	<0.001
+ Health behaviours[c]	407	49950	1	1.26 (0.93, 1.0)	1.68 (1.20, 2.35)	2.41 (1.63, 3.56)	1.65 (1.40, 1.95)	<0.001
+ Illness[d]	459	54655	1	1.29 (0.95, 1.75)	1.69 (1.24, 2.32)	2.93 (1.60, 5.35)	1.68 (1.36, 2.07)	<0.001
Multivariable-adjusted[e]	393	48025	1	1.15 (0.82, 1.62)	1.37 (0.96, 1.94)	2.09 (1.17, 3.71)	1.42 (1.18, 1.71)	<0.001

[a] Cut-points used for FEV_1 were 1.36L, 1.81L, and 2.35L to give approximately equal numbers of disease events in each group

[b] Socioeconomic status comprises occupational social class and educational attainment

[c] Health behaviours include smoking, alcohol consumption, and body mass index

[d] Illness comprises self-rated general health and longstanding illness

[e] Model adjusted for all covariates in the table.

SUPPLEMENTARY TABLE 1. Hazard ratios (95% confidence intervals) for the association between pulmonary function in relation to dementia-related death identified by broad (any mention) and narrow (underlying cause) definitions: individual participant meta-analysis (N = 54,671) of cohort studies from the Health Survey for England (N=4) and the Scottish Health Survey (N=2)

Age- & sex-adjusted Models	**Dementia deaths**	**N**	**Q_1 (highest)**	**Q_2**	**Q_3**	**Q_4 (lowest)**	**Per SD disadvantage**	**P for trend**
Any mention	459	54671	1 (Ref.)	1.32 (0.99, 1.76)	1.78 (1.30, 2.43)	2.74 (1.73, 4.32)	1.65 (1.42, 1.93)	<0.001
Underlying cause	139	54671	1 (Ref.)	1.08 (0.55, 2.14)	1.27 (0.66, 2.47)	1.51 (0.82, 2.81)	1.37 (1.03, 1.82)	0.031

SUPPLEMENTARY TABLE 2. Characteristics of participants according to individual cohort studies: individual participant meta-analysis (N = 54,671) of cohort studies from the Health Survey for England (N=4) and the Scottish Health Survey (N=2)

		Health Survey for England				Scottish Health Survey		
		1995	**1996**	**1997**	**2001**	**1998**	**2003**	**Overall**
Household survey response	%	78	79	76	74	77	67	**-**
Adults irrespective of consent status	N	16055	16443	8582	15647	9040	8092	**73859**
Consented to mortality linkage	%	93.7	93.7	93.9	88.4	86.9	87.9	**91.1**
	N	15036	15411	8060	13835	7857	7114	**67313**
Participants with lung function data (analytic sample)	N	12675	13291	6936	10664	6270	4835	**54671**
Follow-up (years)	mean	14.3	13.5	12.7	9.2	10.6	5.7	**11.7**
	sd	3.4	3.1	2.6	1.5	1.9	0.9	**3.7**
Deaths from any cause	N	2250	2117	985	919	720	336	**7327**
Dementia deaths	N	146	133	67	64	31	18	**459**
Age (years)	mean	46.2	46.2	46.1	47.4	46.2	51.0	**46.8**
	sd	18.1	18.1	17.7	17.6	15.6	17.1	**17.6**
	range	16-100	16-97	16-94	16-99	16-74	16-95	**16-100**
Female	%	53.0	53.1	52.5	53.3	55.2	55.4	**53.4**
Height (cm)	mean	167.4	167.4	167.5	167.6	166.8	166.5	**167.3**
	sd	9.6	9.6	9.6	9.6	9.5	9.5	**9.6**
White British	%	95.1	94.6	95.3	95.2	99.4	98.7	**95.8**
Left school ≥16[a]	%	61.8	63.7	63.8	68.2	61.6	63.6	**63.9**
Non-manual social class	%	56.8	56.1	55.9	58.1	51.8	56.5	**56.2**
Never smoker	%	46.7	46.2	45.7	47.7	44.6	50.1	**46.7**
Drinks alcohol weekly or more often	%	65.2	66.5	66.6	66.5	61.3	61.6	**65.1**
Body mass index	mean	26.0	26.2	26.3	26.9	26.7	27.5	**26.5**
	sd	4.4	4.5	4.7	4.8	4.8	5.1	**4.7**
Self-rated health good or very good	%	77.2	77.2	75.7	76.0	74.9	72.2	**76.1**
Longstanding illness	%	42.0	42.5	44.1	45.6	44.6	45.7	**43.7**

[a] Leaving school at the age of 16 years of younger approximates to completing only compulsory education, despite the changes in minimum school leaving age during the twentieth century

SUPPLEMENTARY TABLE 3. Survey participants who consented and did not consent to record linkage: individual participant meta-analysis (N = 54,671) of cohort studies from the Health Survey for England (N=4) and the Scottish Health Survey (N=2)

	Consented	**Did not consent**	**P**
N	67313	6546	-
Age [mean (SD)]	46.9 (18.0)	47.9 (19.6)	<0.001
Female (%)	54.6	59.1	<0.001
Height, cm [mean (SD)]	167.1 (9.6)	166.2 (9.8)	<0.001
Ethnicity (% non-white British)	95.6	88.1	<0.001
Left school ≥16 years (%)	63.6	62.7	0.176
Non-manual social class (%)	55.4	54.4	0.144
Never smoker (%)	46.4	50.5	<0.001
Drinks alcohol weekly or more often (%)	63.9	56.5	<0.001
Body mass index [mean (SD)]	26.5 (4.7)	26.1 (4.7)	<0.001
Self-rated health good or very good (%)	75.0	72.6	<0.001
Longstanding illness (%)	43.8	40.4	<0.001

SUPPLEMENTARY TABLE 4. Correlation matrix for the three measured lung function tests: individual participant meta-analysis (N = 54,671) of cohort studies from the Health Survey for England (N=4) and the Scottish Health Survey (N=2)

	FEV_1	FVC	Peak flow
FEV_1	1	0.92 P<0.001	0.82 P<0.001
FVC	0.92 P<0.001	1	0.77 P<0.001
Peak flow	0.82 P<0.001	0.77 P<0.001	1

SUPPLEMENTARY TABLE 5. Hazard ratios (95% confidence intervals) for the association between pulmonary function in relation to dementia-related death: individual participant meta-analysis (N = 54,671) of cohort studies from the Health Survey for England (N=4) and the Scottish Health Survey (N=2)

FVC (L)								
Models	**Dementia deaths**	**N**	**Q_1 (highest)**	**Q_2**	**Q_3**	**Q_4 (lowest)**	**Per SD disadvantage**	**P for trend**
Age- & sex-adjusted (basic model)	459	54671	1 (Ref.)	1.40 (0.93, 2.11)	1.84 (1.28, 2.66)	2.90 (1.77, 4.75)	1.52 (1.30, 1.78)	<0.001
+ Height	413	52571	1	1.26 (0.85, 1.88)	1.50 (1.06, 2.13)	2.58 (1.48, 4.48)	1.42 (1.20, 1.68)	<0.001
+ Ethnicity	459	54647	1	1.43 (0.95, 2.14)	1.87 (1.31, 2.69)	2.96 (1.83, 4.79)	1.55 (1.33, 1.80)	<0.001
+ Socioeconomic status[1]	444	51879	1	1.31 (0.87, 1.96)	1.73 (1.14, 2.62)	2.54 (1.49, 4.33)	1.45 (1.19, 1.76)	<0.001
+ Health behaviours[2]	407	49950	1	1.41 (0.98, 2.02)	1.79 (1.26, 2.53)	3.02 (1.97, 4.63)	1.57 (1.34, 1.83)	<0.001
+ Illness[3]	459	54655	1	1.37 (0.89, 2.10)	1.81 (1.20, 2.74)	2.98 (1.65, 5.40)	1.55 (1.26, 1.90)	<0.001
Multivariable-adjusted[4]	393	48025	1	1.24 (0.85, 1.82)	1.54 (1.07, 2.24)	2.65 (1.48, 4.73)	1.41 (1.17, 1.69)	<0.001
PF (L/min)								
Models	**Dementia deaths**	**N**	**Q_1 (highest)**	**Q_2**	**Q_3**	**Q_4 (lowest)**	**Per SD disadvantage**	**P for trend**
Age- & sex-adjusted (basic model)	459	54671	1 (Ref.)	1.53 (1.10, 2.11)	1.98 (1.34, 2.91)	3.31 (2.32, 4.70)	1.62 (1.44, 1.82)	<0.001
+ Height	413	52571	1	1.44 (1.06, 1.95)	2.00 (1.28, 3.11)	3.14 (2.22, 4.45)	1.60 (1.41, 1.81)	<0.001
+ Ethnicity	459	54647	1	1.54 (1.12, 2.12)	2.02 (1.37, 2.98)	3.37 (2.36, 4.80)	1.63 (1.45, 1.83)	<0.001
+ Socioeconomic status[1]	444	51879	1	1.43 (0.99, 2.06)	1.79 (1.20, 2.66)	2.87 (1.94, 4.26)	1.52 (1.34, 1.74)	<0.001
+ Health behaviours[2]	407	49950	1	1.47 (1.08, 2.00)	1.91 (1.32, 2.7)	3.27 (2.31, 4.62)	1.62 (1.43, 1.74)	<0.001
+ Illness[3]	459	54655	1	1.49 (1.05, 2.10)	1.98 (1.28, 3.07)	3.19 (2.12, 4.82)	1.62 (1.39, 1.87)	<0.001
Multivariable-adjusted[4]	393	48025	1	1.31 (0.96, 1.79)	1.66 (1.12, 2.48)	2.54 (1.76, 3.66)	1.46 (1.27, 1.67)	<0.001

[1] Socioeconomic status comprises occupational social class and educational attainment
[2] Health behaviours include smoking, alcohol consumption, and body mass index
[3] Illness comprises self-rated general health and longstanding illness
[4] Model adjusted for all covariates in the table.

SUPPLEMENTARY TABLE 6. Sensitivity analyses – examining the effect of: (a) excluding smokers; (b) excluding deaths occurring in the first 5 years of follow up and (c) accounting for missing data using multiple imputation: individual participant meta-analysis (N = 54,671) of cohort studies from the Health Survey for England (N=4) and the Scottish Health Survey (N=2)

Models	Dementia deaths	N	Q_1 (highest)	Q_2	Q_3	Q_4 (lowest)	Per SD disadvantage	P for trend
Restricted to never-smokers (multivariable adjusted)								
FEV_1	170	21928	1 (Ref.)	1.34 (0.81, 2.22)	1.23 (0.67, 2.25)	1.44 (0.74, 2.80)	1.40 (1.02, 1.92)	0.039
FVC	170	21928	1 (Ref.)	1.35 (0.80, 2.29)	1.40 (0.75, 2.61)	1.70 (0.85, 3.40)	1.26 (0.95, 1.68)	0.11
PF	170	21928	1 (Ref.)	1.75 (1.03, 2.99)	1.62 (0.90, 2.90)	3.26 (1.63, 6.51)	1.43 (1.14, 1.78)	0.002
Early deaths excluded (multivariable adjusted)								
FEV_1	342	48025	1 (Ref.)	1.10 (0.78, 1.54)	1.21 (0.82, 1.79)	1.55 (1.01, 2.38)	1.32 (1.07, 1.64)	0.009
FVC	342	48025	1 (Ref.)	1.20 (0.83, 1.76)	1.35 (0.89, 2.04)	1.92 (1.20, 3.06)	1.29 (1.06, 1.56)	0.012
PF	342	48025	1 (Ref.)	1.24 (0.88, 1.75)	1.38 (0.94, 2.01)	2.24 (1.48, 3.39)	1.37 (1.17, 1.60)	<0.001
Multiple imputation (multivariable adjusted)								
FEV_1	459	54671	1 (Ref.)	1.17 (0.87, 1.57)	1.48 (1.06, 2.06)	2.11 (1.38, 3.22)	1.59 (1.30, 1.93)	<0.001
FVC	459	54671	1 (Ref.)	1.32 (0.85, 2.05)	1.59 (1.12, 2.24)	2.43 (1.48, 3.99)	1.52 (1.25, 1.85)	<0.001
PF	459	54671	1 (Ref.)	1.40 (1.01, 1.94)	1.74 (1.16, 2.60)	2.56 (1.81, 3.62)	1.58 (1.36, 1.84)	<0.001

SUPPLEMENTARY TABLE 7. Survey participants included and excluded from fully-adjusted model: individual participant meta-analysis (N = 54,671) of cohort studies from the Health Survey for England (N=4) and the Scottish Health Survey (N=2)

	Complete data for all variables	**Missing data in ≥1 variable**	**P**
N	48025	6646	-
Age [mean (SD)]	47.4 (16.6)	42.5 (23.2)	<0.001
Female (%)	52.7	59.0	<0.001
Height, cm [mean (SD)]	167.3 (9.5)	166.9 (9.9)	0.010
Ethnicity (% white British)	96.5	91.1	<0.001
Left school ≥16 years (%)	63.4	67.6	<0.001
Non-manual social class (%)	56.4	52.9	<0.001
Never smoker (%)	45.7	54.5	<0.001
Drinks alcohol weekly or more often (%)	66.3	55.3	<0.001
Body mass index [mean (SD)]	26.6 (4.6)	24.0 (4.6)	<0.001
Self-rated health good or very good (%)	77.1	68.4	<0.001
Longstanding illness (%)	43.3	47.1	<0.001